Beyond the lungs: Alpha-1 antitrypsin's potential role in human gestation

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Abstract

Alpha-1 antitrypsin (AAT) is an acute-phase protein with strong inhibitory activity towards proteolytic enzymes, mainly elastase but also trypsin, chymotrypsin and thrombin. The biological role of the protein and the effects of its deficiency have been subjects of scientific research for years, yet in many areas our knowledge remains incomplete. Alpha-1 antitrypsin deficiency (AATD), a defect in AAT synthesis and functionality, is one of the most frequently inherited genetic disorders among Caucasian populations. Its severe form is characterized by very low serum levels of AAT, and it most often affects the lungs (causing early-onset emphysema or chronic obstructive lung disease (COPD)) and/or liver (leading to jaundice and liver cirrhosis in children and adults). However, little is known about other possible clinical consequences of AAT deficiency. We discuss AAT's potential role in mechanisms regulating human fertility and gestation, with a particular emphasis on the clinical context and on indications for AATD diagnostic testing.

Key words: diagnosis, pregnancy, alpha-1 antitrypsin, oocyte maturation, alpha-1 antitrypsin deficiency

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Alpha-1 antitrypsin (AAT) is an acute-phase glycoprotein that functions primarily as a protease inhibitor (PI), acting on elastase, trypsin, chymotrypsin, and thrombin. It is synthesized mainly by hepatocytes and delivered to other tissues via the plasma, with significant action in the lungs, where it protects the alveolar space from proteolytic damage by neutrophil elastase.¹ Alpha-1 antitrypsin deficiency (AATD) is a common inherited genetic disorder among Caucasians. It is estimated that approx. 1 in 3000–4500 individuals suffers from this autosomal codominant condition, which most often manifests itself as very low concentrations of circulating AAT, a consequence of pathogenic mutations in the *SERPINA1* gene.² As might be expected, the disorder mainly affects the lungs (resulting in airflow obstruction, and/or early onset emphysema and/or bronchiectasis), the liver (causing jaundice and/or liver disease of unexplained etiology in newborns, children and adults), and rarely, the skin (manifested as panniculitis). The most common symptoms associated with AATD are widely known and well-documented (Table 1). Despite the fact that classic AATD-related symptoms are quite well-defined, the disease is under-recognized, with less than 10% of the expected number of cases reported, and an average of 5–8 years of delay between the initial symptoms and diagnosis.^{5,6} In addition, current knowledge of other symptoms and clinical consequences of AAT anomalies remains incomplete. Given the large number of studies focused on this protein, such a vague understanding of its functions and the wider implications of its deficiency is cause for concern.

This paper discusses the potential role of AAT in mechanisms regulating human fertility and gestation, with a particular emphasis on the clinical context and indications for diagnostic testing for AATD.

Table 1. The main indications for diagnosing alpha-1 antitrypsin deficiency according to current recommendations^{3,4}

Emphysema, especially with early onset (before 45 years of age)
Symptomatic form of chronic obstructive pulmonary disease, regardless of exposure to tobacco smoke
Bronchial asthma with persistent airway obstruction
Persistent airway obstruction confirmed by function tests and exposure to occupational factors or tobacco smoke, regardless of whether symptoms occur
Bronchiectasis of unclear etiology
Vasculitis with the presence of c-ANCA
Liver disease of unclear etiology
Necrotizing panniculitis
Family members with confirmed alpha-1 antitrypsin deficiency
A family history of one of the aforementioned disorders

The alpha-1 antitrypsin protein and human reproduction

Encoded by the *SERPINA1* gene (MIM #107400), AAT is part of a family of structurally unique serine protease inhibitors, referred to as serpins, implicated

in the pathogenesis of the so-called serpinopathies. These include neurodegenerative diseases, angioedema and coagulation abnormalities.^{6,7} Abnormalities in AAT and other serpins can have a number of consequences.

Serum levels of AAT increase during pregnancy and during estrogen therapy.^{8–10} However, it should be emphasized that pregnancy-related AAT increases in women with severe AATD does not reach levels considered normal. This is of potential clinical importance, as AAT promotes angiogenesis and vascularization of the endometrium, and inhibits the activity of cathepsins, tissue plasminogen activator and kallikrein, implicating it in trophoblast invasion and implantation.^{11–13} Alpha-1 antitrypsin has also been shown to serve in the placenta as a substrate for the human serine protease high temperature requirement A1 (HTRA1), which in turn is supposed to support trophoblast apoptosis.¹⁴ Furthermore, AAT may play a role in fertility regulation, pregnancy loss and other obstetric pathologies.^{15–22} Finally, there is data from maternal serum protein profiling showing that alpha-1-antitrypsin is among the markers for non-invasive prenatal diagnoses of trisomy 21, 18 and 13.²³

Oocyte maturation

Alpha-1 antitrypsin in the follicular fluid (FF) originates from the circulation as well as from follicular secretions. Follicular fluid provides an optimal environment for the development and maturation of the oocyte, and is thought to have an important role in follicular maturation and, as an indicator of oocyte maturity, in controlling the release of mature oocytes.^{24,25} Wu et al. provided preliminary data documenting differences in protein expression profiles (i.e., AAT) in FF between controlled ovarian hyperstimulation (COH) and natural ovulatory cycles.¹⁵ That study included a group of 12 infertile women (6 receiving COH and another 6 with natural cycles) undergoing in vitro fertilization. Alpha-1 antitrypsin concentrations were significantly higher in FF from follicles with immature oocytes than in follicles with mature oocytes. The authors suggested that the higher AAT level in FF from women during the COH cycle may inhibit oocyte maturation, leading to the reduced fertilization rate seen in these patients. It can further be concluded that abnormalities in protein profiles as a result of increased immune and inflammatory responses might be a factor in adverse effects of controlled ovarian hyperstimulation on oocyte vitality, contributing to poor in vitro fertilization and embryo transfer outcomes.

Spontaneous abortions

Changes in AAT concentration are a relevant factor in spontaneous as opposed to elective abortions.¹⁶

In a prospective case-control study, serum levels of AAT and cytokines were assessed in 14 patients with recurrent spontaneous abortions, 15 with sporadic spontaneous abortions and 11 controls who had undergone elective abortions of normal pregnancies. Women with recurrent and sporadic pregnancy loss had significantly lower AAT concentrations than those with normal pregnancies. However, antiproteolytic activity was significantly lower in the elective abortion and sporadic abortion groups. Interestingly, in both spontaneous abortion groups, these findings were accompanied by elevated levels of circulating proinflammatory cytokines.

Preeclampsia

Preeclampsia (PE) affects 2–8% of pregnancies and is characterized by hypertension and proteinuria after 20 weeks of gestation.²⁶ It is classified as early-onset preeclampsia (EOPE) if it results in a preterm delivery before 34 weeks of gestation. The mechanisms governing PE are still not fully understood. Some recently identified factors include alpha-1-antitrypsin, postulated as a protective factor acting by activating Smad2 and the inhibitor of DNA binding 4 and/or by suppressing oxidative stress via down-regulation of the p38MAPK signaling pathway.^{27,28}

Preeclampsia and in particular EOPE are characterized by high mortality rates. Therefore, the identification of novel, sensitive prognostic biomarkers is of particular interest. Kolialexi et al. demonstrated a 3-fold increase in plasma concentrations of AAT in prospectively analyzed samples from 10 women with subsequent EOPE, compared with those of 40 controls with normal pregnancies, matched for gestational age and duration of sample storage.²² This is in line with other reports of significantly increased AAT levels in patients with clinical symptoms of severe PE vs those with uncomplicated pregnancies.^{19,29,30} Obviously, this might simply result from inflammatory components of pregnancies complicated by EOPE, but AAT should also be considered a candidate biomarker or part of a biomarker panel in early screening for EOPE.

Interestingly, for PE per se, the published data on plasma levels of AAT are contradictory. Twina et al. prospectively analyzed the link between a relative decline in AAT levels and enzymatic activity in maternal blood from PE and normal-pregnancy patients.¹⁸ They analyzed samples from 41 individuals (singleton pregnant females within 24–42 weeks of gestation), including 23 patients with severe preeclampsia and 18 patients without preeclampsia who were admitted in labor. Severe PE was defined as hypertension associated with any of the following: proteinuria after 20 weeks of pregnancy and systolic blood pressure > 160 mm Hg and/or diastolic blood pressure > 110 mm Hg, severe proteinuria (≥ 5 g per day), or multi-organ involvement. The authors documented significantly lower AAT concentrations and activity among

patients with severe PE compared to parturient women without PE.

Feng et al., who looked at differences in protein expression profiles between normal full-term pregnancy, early-onset severe preeclampsia (ES-PE) and late-onset severe preeclampsia (LS-PE), obtained very similar results.¹⁹ A cohort of 30 patients (10 per group) was included in the study, and a total of 20 differentially expressed proteins were identified; AAT expression differed among the 3 groups. Its level was the highest in the normal full-term pregnancy group (1.85 ± 0.15 g/L), moderate in the ES-PE group (0.77 ± 0.14 g/L) and lowest in the LS-PE group (0.42 ± 0.07 g/L; $p < 0.05$).

Preterm labor

Alpha-1 antitrypsin expression in the amnion, which is the inner layer of the fetal membrane lining the amniotic cavity, is regulated by cytokines (such as tumor necrotic factor alpha, interleukin-6 and oncostatin M).³¹ Izumi-Yoneda et al. noted that in amnion from pregnancies with premature rupture of the membrane (PRM), AAT activity was significantly lower, probably as a result of its oxidation.³¹ Thus, an imbalance between oxidation and AAT expression/activity may contribute to PRM.

Deficiency in AAT, as a protective factor against tissue damage from enzymes released by inflammatory cells, has also been proposed by Baron et al. to be involved in preterm labor, in PRM and preterm PRM (PPRM).²¹ Their study defined PRM as rupture of membranes at least 1 h prior to the onset of labor or after 37 weeks of gestation, and PPRM as PRM prior to 37 weeks of gestation. The authors measured AAT concentration and activity in blood samples from 71 patients in a prospective case-control study. No significant differences in circulating AAT levels or activity were detected between patients with preterm and term labor, or between those with PRM and those with PPRM. AAT deficiency was observed in only 2 women, who, notably, belonged to the 15-patient PPRM group. Taking into account that inherited AAT deficiency is largely underdiagnosed, the authors suggested further investigation into whether AATD is undetected in pregnant women and affects the risk of obstetric complications.

However, to the best of our knowledge, pregnancy-related issues in women diagnosed with AATD have not been described to date. Of course, such issues may not occur, but a possible reason is that when AATD is eventually recognized, it is usually beyond the 5th decade of life, due to a progressive decline in lung function or to emphysema. During the first 4 decades of life, the major health problem of affected individuals may be liver dysfunction (in the form of chronic elevation of liver enzymes or cirrhosis). In other words, symptoms of AATD would not commonly be expected during the usual range of child-bearing years.

Alpha-1 antitrypsin deficiency awareness in obstetrics

To expand our current knowledge of possible and rare clinical consequences associated with decreased AAT, and following the current recommendations (Table 1), we would like to encourage gynecologists and obstetricians to check serum concentrations of AAT in female patients with persistent airflow obstruction (as demonstrated by spirometry), a family history of emphysema (particularly in individuals ≤ 45 years) and/or unexplained chronic liver disease, or a positive family history of AATD.

It is important to bear in mind that the optimal counseling time for determining genetic risk and carrier status, introducing prophylactic factors and discussing the availability of prenatal testing is before pregnancy. An AATD diagnosis should also be considered in neonates and infants with prolonged jaundice after birth and/or abnormal liver enzymes.

It should be noted that AATD diagnosis is available in Poland and relatively simple. All subjects with serum concentrations of AAT protein below 100 mg/dL should be referred for more detailed testing. This consists of phenotyping and genotyping or sequencing and is easily performed from blood spot samples (whole blood samples dried on dedicated blotting paper). These samples can be delivered by regular post. Since 2009, the National Institute of Tuberculosis and Lung Diseases in Warsaw, Poland has been providing a nationwide testing program, free of charge for all patients with respiratory disorders.³²

Conclusions

There is evidence that AAT plays a role in early-onset preeclampsia and fetal loss. Consequently, the potential of AAT as a biomarker for identifying patients at increased risk of EOPE needs further investigation. On the other hand, severe AATD in mothers or fetuses does not seem to affect conception or pregnancy outcomes, respectively. Nevertheless, it is advisable to consider testing for AATD (serum concentrations of AAT and/or *SERPINA1* gene analyses) in female patients with a personal or family history of chronic respiratory disorders and/or chronic liver pathology.

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